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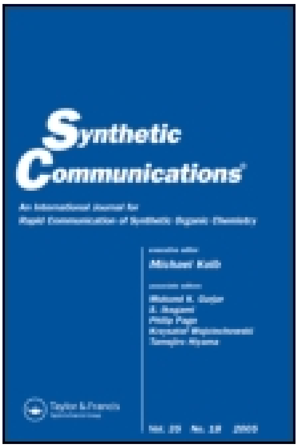

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Sc(OTf)$_3$: A Highly Efficient and Renewable Catalyst for Michael Addition of Indoles to Nitroolefins in Water

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$Sc(OTf)_3$: A HIGHLY EFFICIENT AND RENEWABLE CATALYST FOR MICHAEL ADDITION OF INDOLES TO NITROOLEFINS IN WATER

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Man Wang, and Yiqian Wan**
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Guangzhou, China*

A catalytic amount of scandium trifluoromethanesulfonate [$Sc(OTf)_3$] (2.5 mol%) was used to catalyze the Michael addition of indoles to nitroolefins in water to afford the corresponding 3-alkylated indoles in good to excellent yields. The short reaction times, excellent yields, and renewability of the catalyst are noteworthy.

Keywords: Lewis acid; Michael addition; renewable catalyst; scandium trifluoromethanesulfonate; water

INTRODUCTION

In recent years, significant efforts have been dedicated to carrying out catalytic organic reactions in water, because water is cheap, safe, and environmentally benign.[1] In addition, when using water as solvent, many reactions illustrate unique reactivities and selectivities that are not usually observed in organic media.[2] Thus, the development of organic reactions in water has received increasing attention.

Indole and many of its derivatives are present in many natural products and synthetic materials that possess biological and pharmacological activities.[3] Because 3-alkylated indoles are versatile intermediates for the synthesis a wide range of indoles derivatives,[4] several methods for the preparation of indole derivatives were established by means of easy electrophilic replacement reactions of the 3-position of indoles. Lewis acid–catalyzed[5] Michael addition of indoles to enones or nitroolefins synthesizes 3-alkylated indoles; however, a large amount of the catalyst (10 mol%) and long reaction times (several hours) are often required. Furthermore, most of the reactions are carried out in organic solvents. In recent years, although other catalysts such as $[Al(DS)_3] \cdot 3H_2O$ (DS = dodecyl sulfate),[6] heteropoly acid,[7] carbohydrate-based tolylsulfonyl hydrazines,[8] and β-cycoldextrin[9] were used for these reactions in water, the main drawbacks (high catalyst loading and long reaction times) still remained. Very recently, Yao reported catalyst-free conjugative addition of indoles to β-nitrostyrenes in water,[10] but high temperature (100 °C)

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and several hours were still required to reach full conversion of β-nitrostyrenes. Therefore, the development of a highly efficient and environmentally friendly catalyst to perform the reaction under mild conditions, in particular, at room temperature and in a short time, would be valuable.

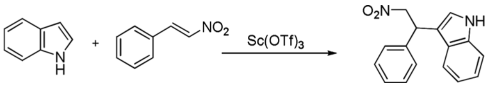
$Sc(OTf)_3$, as a commercially available, water-tolerant, and reusable Lewis acid, was reported to successfully catalyze many synthetic organic reactions in both organic solvents and aqueous media, even pure water.[11] It was also reported to catalyze Friedel–Crafts conjugate addition of indoles, by Mannabe and Kawatsura groups, respectively.[12,13] However, $Sc(OTf)_3$ showed less catalytic activity than $Sc(DS)_3$ in water. While Kawatsura and coworkers reported that $Sc(OTf)_3$ as well as $Hf(OTf)_4$ can effectively catalyze this reaction in CH_3CN, they mainly focused on the addition reactions of indoles to carbonyls. In this article, we report the remarkable catalytic activity of $Sc(OTf)_3$ for the conjugate addition of indoles to nitroolefins in water.

RESULTS AND DISCUSSION

Initially, the conjugate addition of indole to β-nitrostyrene was carried out in the presence of $Sc(OTf)_3$ (10 mol%) in water at 30 °C. Fortunately, the reaction was completed in only 10 min. When the catalyst loading was decreased to 2.5 mol%, the reaction also finished in the same time, and excellent yield was afforded. However, when the amount of the catalyst was reduced to 2 mol%, the β-nitrostyrene could not be completely consumed within 10 min and the yield decreased to 90%. In contrast, the reaction was also carried out in the absence of catalyst, but the yield was only a trace, even with prolonging reaction time. These results are summarized in Table 1.

To test the chemoselectivity of indoles reacting with nitrostyrenes over enones, we performed a reaction mixing indole (1 mmol), β-nitrostyrene (0.5 mmol), and 2-cyclopenten-1-one (0.5 mmol) under almost the same conditions as mentioned previously except time was prolonged to 100 min. The gas chromatography/mass

Table 1. Effect of the catalyst loading on the Michael addition of indole to β-nitrostyrene[a]



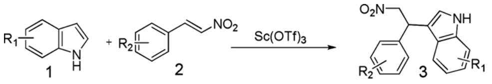
Entry	$Sc(OTf)_3$ (mol%)	Time (min)	Yield (%)[b]
1	10.0	10	97
2	5.0	10	95
3	2.5	10	95
4	2.5	100	80[c]
5	2.0	10	90
6	–	1440	Trace

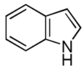
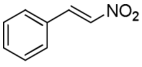
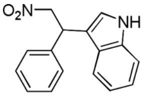
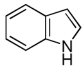
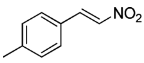
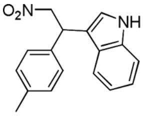
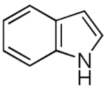
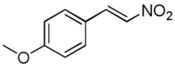
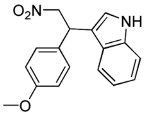
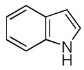
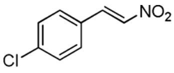
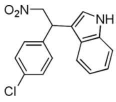
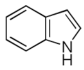
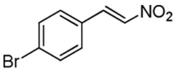
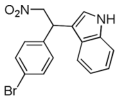
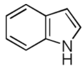
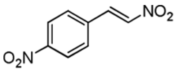
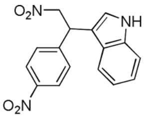
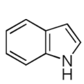
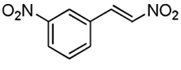
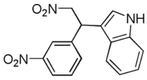
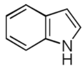
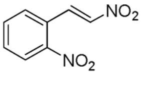
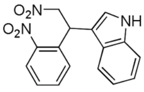
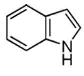
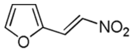
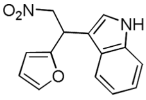
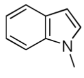
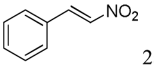
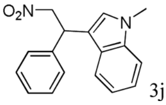
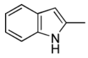
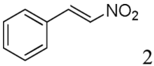
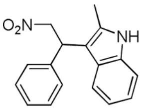
[a] All reactions were performed in water at 30 °C.

[b] Isolated yield.

[c] 1 Equiv 2-cyclopenten-1-one based on β-nitrostyrene was added.

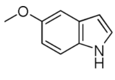
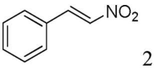
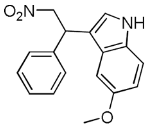
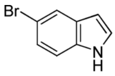
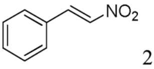
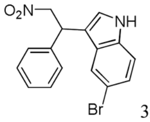
Table 2. Michael addition of indoles to nitroolefins catalyzed by $Sc(OTf)_3$ in water[a]



Entry	Indoles	Nitroolefins	Product	Time (min)	Yield (%)[b]
1	 1a	 2a	 3a	10	95
2	 1a	 2b	 3b	60	97
3	 1a	 2c	 3c	120	91
4	 1a	 2d	 3d	10	92
5	 1a	 2e	 3e	70	93
6	 1a	 2f	 3f	30	90
7	 1a	 2g	 3g	15	92
8	 1a	 2h	 3h	1200	87
9	 1a	 2i	 3i	15	94
10	 1b	 2a	 3j	1440	91
11	 1c	 2a	 3k	10	93

(*Continued*)

Table 2. Continued

Entry	Indoles	Nitroolefins	Product	Time (min)	Yield (%)[b]
12	 1d	 2a	 3l	10	94
13	 1e	 2a	 3m	70	91

[a]All reactions were carried out with 2.5 mol% $Sc(OTf)_3$ at 30 °C, and were stopped when nitroolefins were consumed.
[b]Isolated yield.

spectrometry (GC/MS) analysis of the reaction mixture showed 4.21% of β-nitrostyrene, 22.8% of 2-cyclopenten-1-one, and 72.24% and 0.75% of their corresponding 3-alkylated indole products. Moreover, only 3-(2-nitro-1-phenylethyl)-1*H*-indole (3a) was isolated in 80% yield (Table 1, entry 4). Hence, $Sc(OTf)_3$ is a highly chemoselective catalyst in this reaction system.

A variety of indoles and nitroolefins were synthesized using $Sc(OTf)_3$ (2.5 mol%) as the catalyst in water at 30 °C to investigate the scope of the substrates (Table 2). As demonstrated in Table 2, all the conjugate adducts were obtained in good to excellent yields, but the reaction times were varied according to the substituents on the olefins and indoles. For the olefins, the electron-donating substitutes such as methyl and methoxy led to the formation of the corresponding products with longer reaction times (Table 2, entries 2 and 3). On the other hand, the nitrostyrenes bearing electron-withdrawing groups except the bromo group reacted smoothly in short reaction times (within 30 min) to afford their corresponding products (Table 2, entries 4–7). In the case of 1-nitro-2-(2-nitrovinyl)-benzene, the yield was slightly less and needed a longer reaction time, which might result from the steric hindrance (Table 2, entry 8). Furthermore, the nitroolefin containing an acid-sensitive moiety could also be transformed to the desired product in excellent yield under the present reaction conditions (Table 2, entry 9). The indoles, such as 2-methylindole and 5-methoxyindole, could react with β-nitrostyrenes to afford the expected products in excellent yield only within 10 min, probably because of the electron-rich groups, which can increase the electron density of the indole ring to accelerate the reactions (Table 2, entries 11 and 12), whereas the indole rings bearing electron-withdrawing groups such as 5-bromoindole needed a longer time to complete the reaction (Table 2, entry 13). Interestingly, *N*-methylindole required longer time than 2-methyl-indole to obtain the corresponding product. This could be attributed to the fact that the free N-H of indole, which played an essential role in activating the indole ring by $Sc(OTf)_3$, was occupied (Table 2, entries 10 vs. 11).

Because $Sc(OTf)_3$ is more soluble in water than in organic solvents, and because the catalyst could be recovered almost quantitatively in the aqueous layer,[7] we also carried out consecutive Michael addition reactions between indole and

Table 3. Recycling Michael addition of indole to nitroolefins catalyzed by the amount of 2.5 mol% $Sc(OTf)_3$[a]

Run	1	2	3	4	5
Time (min)	10	10	10	10	10
Yield (%)[b]	95	93	92	92	88

[a] All reactions were carried out in water at 30 °C.

[b] Isolated yield.

β-nitrostyrene to test the renewability of the catalyst (Table 3). After the initial experiment, the organic compounds were carefully extracted with Et_2O, and the residue Et_2O in the water phase was removed in vacuum. The resulting mixture was then used in the next run. The catalytic activity of the catalyst was so remarkable that the yield had only a little decrease even after five runs.

CONCLUSIONS

In summary, we have developed a simple and efficient method for Michael addition of indoles to nitroolefins using catalytic amount of $Sc(OTf)_3$ (2.5 mol%). The reactions were performed well at 30 °C in less than 100 min, with several exceptions, to provide the desired products in good to excellent yields without any by-products. Moreover, the catalyst can be renewed without significantly decreasing activities.

EXPERIMENTAL

$Sc(OTf)_3 \cdot xH_2O$, indoles, and nitroolefins were commercially available and used as received. Column chromatography was performed with silica gel (200–300 mesh) purchased from Qingdao Haiyang Chemical Co. Ltd. Thin-layer chromatography (TLC) was carried out with Merck silica-gel GF254 plates. All products were characterized by MS, ^1H NMR, and ^{13}C NMR, which were compared with the previously reported data. ^1H NMR and ^{13}C NMR spectra were recorded at room temperature on a Varian Mercury Plus 300 instrument at 300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR with solvent as reference. Liquid chromatography mass spectra (LCMS) were recorded on a Shimadzu LCMS-2010A instrument. Electron impact–mass (EI-MS) spectra were recorded on a Thermo Trace DSQ El mass spectrometer.

General Procedure for the Michael Addition of Indoles to Nitroolefins in Water

Indole (1 mmol) and β-nitrostyrene (0.5 mmol) were added to a solution of $Sc(OTf)_3 \cdot xH_2O$ (2.5 mol%) in 1 ml water. The mixture was stirred at 30 °C, and the reaction was monitored by TLC until the starting material was consumed. The mixture was then diluted with water and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4.

The solvent was concentrated in vacuum, and the residue was purified by column chromatography on silica gel (ethyl acetate–petroleum ether) to give the target products.

General Procedure for the Recycling of the Catalyst

The Michael addition of indole to β-nitrostyrene was carried out as described in the general procedure. After 10 min, the reaction mixture was extracted with diethyl ester (4 × 2 mL), and the residual diethyl ester in water phase was removed in a vacuum. Then indole and β-nitrostyrene were added to the aqueous layer for the second run. This process was then repeated.

Data

3-(2-Nitro-1-phenylethyl)-1*H*-indole (3a). Mp 98–99 °C (lit.[14] mp 97–99 °C). ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.95 (dd, $J = 12.3$, 8.4 Hz, 1H), 5.08 (dd, $J = 12.3$, 7.5 Hz, 1H), 5.21 (t, $J = 7.8$ Hz, 1H), 7.03 (d, $J = 2.4$ Hz, 1H), 7.09 (t, $J = 7.5$ Hz, 1H), 7.21 (t, $J = 7.5$ Hz, 1H), 7.28–7.38 (m, 5H), 7.45 (d, $J = 7.8$ Hz, 1H), 8.07 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 41.5, 79.5, 111.3, 114.1, 118.7, 119.8, 121.5, 122.5, 125.9, 127.4, 127.6, 128.8, 136.3, 139.0. ESI-MS: $m/z = 265$ $[M-H]^-$.

3-(2-Nitro-1-*p*-tolylethyl)-1*H*-indole (3b). Oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.34 (s, 3H), 4.93 (dd, $J = 12.3$, 8.4 Hz, 1H), 5.06 (dd, $J = 12.0$, 7.5 Hz, 1H), 5.17 (t, $J = 8.1$ Hz, 1H), 7.01–7.24 (m, 7H), 7.35 (d, $J = 8.4$ Hz, 1H), 7.46 (d, $J = 8.1$ Hz, 1H), 8.07 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 21.0, 41.2, 79.5, 111.3, 114.3, 118.7, 119.7, 121.4, 122.4, 125.9, 127.4, 129.4, 136.0, 136.3, 136.9. ESI-MS: $m/z = 279$ $[M-H]^-$.

3-(1-(4-Methoxyphenyl)-2-nitroethyl)-1*H*-indole (3c). Mp 149–150 °C (lit.[15] mp 149–150 °C). ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.79 (s, 3H), 4.90 (dd, $J = 12.0$, 8.4 Hz, 1H), 5.05 (dd, $J = 12.0$, 7.2 Hz, 1H), 5.15 (t, $J = 8.1$ Hz, 1H), 6.85 (d, $J = 8.7$ Hz, 2H), 7.02–7.11 (m, 2H), 7.17–7.26 (m, 3H), 7.36 (d, $J = 8.1$ Hz, 1H), 7.43 (d, $J = 8.1$ Hz, 1H), 8.07 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 40.9, 55.2, 79.7, 111.3, 114.1, 114.5, 118.8, 119.7, 121.3, 122.5, 125.9, 128.7, 131.1, 136.3, 158.6. ESI-MS: $m/z = 295$ $[M-H]^-$.

3-(1-(4-Chlorophenyl)-2-nitroethyl)-1*H*-indole (3d). Mp 107–108 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.91 (dd, $J = 12.6$, 8.4 Hz, 1H), 5.06 (dd, $J = 12.6$, 7.2 Hz, 1H), 5.18 (t, $J = 8.1$ Hz, 1H), 7.02 (d, $J = 2.1$ Hz, 1H), 7.09 (t, $J = 7.5$ Hz, 1H), 7.22 (t, $J = 8.1$ Hz, 1H), 7.28–7.42 (m, 5H), 8.10 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 41.0, 79.2, 111.4, 113.7, 118.6, 119.9, 121.4, 122.7, 125.7, 128.9, 129.0, 133.2, 136.3, 137.6. ESI-MS: $m/z = 299$ $[M-H]^-$.

3-(1-(4-Bromophenyl)-2-nitroethyl)-1*H*-indole (3e). Mp 121–122 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.91 (dd, $J = 12.3$, 8.7 Hz, 1H), 5.06 (dd, $J = 12.3$, 7.2 Hz, 1H), 5.16 (t, $J = 7.8$ Hz, 1H), 7.02–7.11 (m, 2H), 7.20–7.46 (m, 7H), 8.11 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 40.9, 79.1, 111.4, 113.5, 118.6, 119.9, 121.3, 121.4, 122.6, 125.7, 129.3, 131.8, 136.3, 138.1. ESI-MS: $m/z = 343$ $[M-H]^-$.

3-(2-Nitro-1-(4-nitrophenyl)ethyl)-1*H*-indole (3f). Mp 142–143 °C (lit.[16] mp 142 °C). ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.00 (dd, $J = 12.9$, 9.0 Hz, 1H), 5.11 (dd, $J = 12.9$, 6.9 Hz, 1H), 5.28–5.34 (m, 1H), 7.06–7.12 (m, 2H), 7.21–7.24 (m, 1H), 7.36–7.41 (m, 2H), 7.52 (d, $J = 8.4$ Hz, 2H), 8.18 (d, $J = 8.4$ Hz, 2H), 8.25 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 41.2, 78.7, 111.6, 112.7, 118.3, 120.1, 121.5, 122.9, 124.0, 125.5, 128.6, 136.3, 146.6, 147.1. ESI-MS: $m/z = 310$ $[M - H]^-$.

3-(2-Nitro-1-(3-nitrophenyl)ethyl)-1*H*-indole (3g). Oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.01 (dd, $J = 12.9$, 8.7 Hz, 1H), 5.12 (dd, $J = 12.6$, 6.9 Hz, 1H), 5.29–5.24 (m, 1H), 7.07–7.12 (m, 2H), 7.20–7.25 (m, 1H), 7.28 (d, $J = 8.7$ Hz, 2H), 7.51 (t, $J = 7.8$ Hz, 1H), 7.71 (d, $J = 7.8$ Hz, 1H), 8.11–8.15 (m, 1H), 8.20 (s, 1H), 8.24 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 41.0, 78.7, 111.6, 112.6, 118.2, 120.0, 121.5, 122.4, 122.5, 122.8, 125.4, 129.7, 133.9, 136.2, 141.4, 148.3. ESI-MS: $m/z = 310$ $[M - H]^-$.

3-(2-Nitro-1-(2-nitrophenyl)ethyl)-1*H*-indole (3h). Mp 113–114 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.05–5.18 (m, 2H), 5.88 (t, $J = 7.8$ Hz, 1H), 7.02–7.07 (m, 1H), 7.15–7.22 (m, 2H), 7.29–7.53 (m, 5H), 7.90 (d, $J = 7.8$ Hz, 1H), 8.18 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 36.3, 78.1, 111.4, 112.4, 118.4, 119.9, 121.9, 122.7, 124.8, 125.7, 128.4, 129.7, 133.1, 133.5, 136.2, 149.3. ESI-MS: $m/z = 310$ $[M - H]^-$.

3-(1-(Furan-2-yl)-2-nitroethyl)-1-methyl-1*H*-indole (3i). Mp 68–69 °C (lit.[16] mp 69 °C). ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.93 (dd, $J = 12.3$, 7.8 Hz, 1H), 5.07 (dd, $J = 12.6$, 8.1 Hz, 1H), 5.26 (t, $J = 7.8$ Hz, 1H), 6.16–6.18 (m, 1H), 6.31–6.33 (m, 1H), 7.11–7.25 (m, 3H), 7.37–7.39 (m, 2H), 7.56 (d, $J = 8.1$ Hz, 1H), 8.17 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 35.7, 77.8, 107.2, 110.3, 111.3, 111.5, 118.5, 119.9, 122.4, 122.6, 125.5, 136.1, 142.1, 151.9. ESI-MS: $m/z = 255$ $[M - H]^-$.

1-Methyl-3-(2-nitro-1-phenylethyl)-1*H*-indole (3j). Mp 94–95 °C (lit.[14] mp 95–97 °C). ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.76 (s, 3H), 4.95 (dd, $J = 12.3$, 8.4 Hz, 1H), 5.07 (dd, $J = 12.3$, 7.5 Hz, 1H), 5.20 (t, $J = 7.8$ Hz, 1H), 6.87 (s, 1H), 7.06–7.11 (m, 1H), 7.21–7.37 (m, 7H), 7.46 (d, $J = 7.8$ Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 32.6, 41.4, 79.4, 109.4, 112.6, 118.9, 119.3, 122.1, 126.3, 126.4, 127.4, 127.6, 128.8, 137.2, 139.3. EI-MS: $m/z = 280$ $[M]^+$.

2-Methyl-3-(2-nitro-1-phenylethyl)-1*H*-indole (3k). Mp 101–102 °C (lit.[14] mp 103–104 °C). ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.42 (s, 3H), 5.12–5.26 (m, 3H), 7.01–7.14 (m, 2H), 7.25–7.39 (m, 7H), 7.89 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 11.8, 40.4, 78.5, 108.5, 110.6, 118.3, 119.5, 121.0, 126.6, 126.9, 127.1, 128.5, 132.8, 135.1, 139.3. EI-MS: $m/z = 280$ $[M]^+$.

5-Methoxy-3-(2-nitro-1-phenylethyl)-1*H*-indole (3l). Mp 114–115 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.79 (s, 3H), 4.94 (dd, $J = 12.3$, 8.4 Hz, 1H), 5.06 (dd, $J = 12.3$, 7.5 Hz, 1H), 5.15 (t, $J = 7.8$ Hz, 1H), 6.84 (s, 1H), 6.87 (d, $J = 2.4$ Hz, 1H), 7.01 (d, $J = 2.4$ Hz, 1H), 7.23–7.34 (m, 5H), 7.99 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 41.5, 55.8, 79.4, 100.7, 112.0, 112.5, 113.8, 122.2, 126.4, 127.4, 127.6, 128.7, 131.4, 139.0, 153.9. ESI-MS: $m/z = 295$ $[M - H]^-$.

5-Bromo-3-(2-nitro-1-phenylethyl)-1*H*-indole (3m). Mp 121–122 °C (lit.[5e] mp 116–120 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.92 (dd, $J = 12.3, 8.1$ Hz, 1H), 5.04 (dd, $J = 12.3, 8.1$ Hz, 1H), 6.14 (t, $J = 8.1$ Hz, 1H), 7.07 (d, $J = 2.7$ Hz, 1H), 7.21–7.37 (m, 7H), 7.55 (s, 1H), 8.16 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.3, 79.3, 112.8, 113.1, 113.8, 121.2, 122.6, 125.4, 127.5, 127.6, 127.7, 128.9, 134.9, 138.5. ESI-MS: $m/z = 343\ [M - H]^-$.

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